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A personal note on the technique of discovery.

Last Thursday I was preoccupied with an insight into an approach to chemotherapeutic screening. It may be almost commonplace, and its parts are not novel, butin toto the time may be ripe for it. (See proposal dated 11/30/56 to Bristol Co.—J Lein) I had an opportunity to examine the technique of scientific generalization, and to realize that this has been my own principal method of discovery.

The chain of thought here started from the specific questions: what would be the most likely derivatives of DAP to serve as potential antagonists, and how should they be isolated. C-chlorinated and -alkylated products suggested themselves. But if they had to be synthesized from separate precursors, there would be a tedious chemical job. How about making them from DAP itself which is commercially available? But this is rather expensive, why not use DAP isolated from culture filtrates or from cell walls? But actually, is it necessary to isolate the DAP first, when not use the walls directly? Then generalization: would not this approach cover more difficult materials (e.g/ the heptoses and the lipids and the aminosugars)? In fact, even unknown constituents, wall or not.

Further generalization, have crude natural products of various origin even been used as empirical starting materials for specifically screenable activities?

It then occurred to me that this had been a general pattern in my scientific work. Steps:

a) Consider a specific, sometimes a minor technical problem. Because it is restricted, it can be analyzed in its essentials, or else intuitively solved.

b) What are the essentials, expressed in the most general form? [Example: replica plating is equivalent to multi-tube selection].

and

c) What problems of general import can be solved by this technique? Example: selection for specific genotypes , as used in Neurospora reversion studies, is also applicable to selection for rare recombinants. Example: one cycle of enrichment in replica plating can be reiterated for effective indirect selection. Example: pneumococcus transformation & Salmonella transduction are aspects of same phenomenon; lysogenic conversion is correlated at even a further level. Example: hypertonic sucrose might protect against lysis by other agents besides lysozyme.
Not all problems and discoveries are technical. In many cases one has, rather, to frame specific hypotheses and find critical experiments to decide between them. Abstraction is of course a necessary precedent to imagination here too. But I am not sure this has been my strongest technique.

Moral: Solve specific problems, narrow enough to be grappled with. The stimulus of this accomplishment, the abstraction of the technique, and its broader application will then usually suggest other soluble problems and approaches.

I think that this mental cast has something to do with two ways of science (as I think Seymour quoted from Luria): (1) to start with a methodology and find phenomena; (2) to start with a phenomenon and find a rule. Not many people do both well: the biophysicists have generally prospered with (2), which is also safer for graduate students; my own actual emphasis has been on (1). If this is a reflection of talent, it might be better if I did not stick too long with the study of the various systems I uncover, which I have perhaps done or thought I had done.